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Condensation:

Two-stage screening for preterm-preeclampsia offers a cost-saving alternative to one-stage screening.

Short version of title: Preterm preeclampsia screening

AJOG at a Glance

A. First-trimester screening by a combination of maternal factors and three biomarkers identifies a high proportion of pregnancies that develop preterm-preeclampsia. The study explores the possibility of carrying out first-stage screening in the whole population by some of the biomarkers and proceeding to second-stage screening by the triple test only for a subgroup of the population selected on the basis of the risk derived from first-stage screening.

B. Similar screen positive and detection rates can be achieved with a two-stage strategy of screening, if some of the biomarkers are included in the first-stage to select only 20-40% of the population in need of the complete triple test.

C. Two-stage screening and biomarker testing for only part of the population will have financial benefits over conducting the test for the entire population.

ABSTRACT

Background Screening for preeclampsia (PE) at 11-13 weeks' gestation by a combination of maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PlGF) (triple test) can predict about 90% of PE, with delivery at <32 weeks (early-PE), and 75% of PE with delivery at <37 weeks (preterm-PE), at a screen positive rate (SPR) of 10%. In pregnancies identified as being at high-risk for PE by such screening, administration of aspirin (150 mg/day from 11-14 weeks' gestation to 36 weeks) reduces the rate of early-PE by about 90% and preterm-PE by about 60%. Recording of maternal history and blood pressure are part of routine prenatal care but measurement of UtA-PI and PlGF require additional costs.

Objective: To explore the possibility of carrying out first-stage screening in the whole population by maternal factors alone or a combination of maternal factors, MAP and UtA-PI or maternal factors, MAP and PlGF and proceeding to second-stage screening by the triple test only for a subgroup of the population selected on the basis of the risk derived from first-stage screening.

Study design: The data for this study were derived from prospective non-intervention screening for PE at 11^{+0} – 13^{+6} weeks' gestation in 61,174 singleton pregnancies. Patient-specific risks of delivery with PE at <37 and <32 weeks' gestation were calculated using the competing risks model to combine the *prior* distribution of the gestational age at delivery with PE, obtained from maternal characteristics and medical history, with various combinations of multiple of the median (MoM) values of MAP, UtA-PI and PlGF. We estimated the detection rate

(DR) of preterm-PE and early-PE at overall SPR of 10%, 15% and 20%, from a policy in which first-stage screening of the whole population is carried out by some of the components of the triple test and second-stage screening by the full triple test on women selected on the basis of results from first-stage screening.

Results: If the method of first-stage screening is maternal factors, then measurements of MAP, UtA-PI and PlGF can be reserved for only 70% of the population achieving similar DR and SPR as with screening the whole population with the triple test. In the case of first-stage screening by maternal factors, MAP and UtA-PI, then measurement of PlGF can be reserved for only 30-40% of the population and if first-stage screening is by maternal factors, MAP and PlGF, measurement of UtA-PI can be reserved for only 20-30% of the population. Empirical results were consistent with model-based performance.

Conclusions: Two-stage screening and biomarker testing for only part of the population will have financial benefits over conducting the test for the entire population.

Key words: First trimester screening, Preeclampsia, Aspirin, Bayes theorem, Contingent screening, Survival model, Uterine artery Doppler, Mean arterial pressure, Placental growth factor.

INTRODUCTION

Identification of pregnancies at high-risk of developing preeclampsia (PE) at 11-13 weeks' gestation is beneficial because in such cases prophylactic use of aspirin (150 mg/day from 11-14 weeks' gestation to 36 weeks) reduces the rate of early-PE, with delivery at <32 weeks, by about 90% and preterm-PE, with delivery at <37 weeks, by about 60%; but there is little evidence of a reduction in incidence of PE with delivery at term.[1,2] Such screening and treatment is also associated with a reduction in length of stay in the neonatal intensive care unit by about 70%.[3]

The established method of screening for PE is to identify risk factors from maternal demographic characteristics and medical history; in the presence of such factors the patient is classified as high-risk and in their absence as low-risk.[4,5] The performance of this approach of screening is poor [6-8] and, though it is simple, it does not quantify individual patient specific risks. An alternative way of screening is to use logistic regression models fitted to maternal characteristics and medical history alone or in combination with biomarkers to predict early, late or all PE.[9-13] Such models are useful in quantifying the individual patient specific risk for PE, rather than just classifying women into high- and low-risk groups. However, they do not allow the flexibility of selecting different gestational age cut-offs for categorizing the severity of PE, they do not take into account the increasing effect of biomarkers with severity of the disease and they cannot be easily expanded to include additional biomarkers measured at different stages in pregnancy. We have proposed a competing risks approach which allows estimation of the individual

patient-specific risks of PE before any specified gestation and in the interval between any two gestational ages by a combination of maternal characteristics and medical history with biomarkers obtained either individually or in combination at any stage in pregnancy.[6,14-16] Screening by the competing risks approach at 11-13 weeks' gestation by a combination of maternal characteristics and medical history with mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PlGF) can predict about 90% of early-PE and 75% of preterm-PE, at screen positive rate (SPR) of 10%.[6,7,16,17] Recording maternal characteristics and medical history, measurement of blood pressure and hospital attendance at 11-13 weeks' gestation for an ultrasound scan are an integral part of routine antenatal care in many countries. In contrast, measurements of serum PlGF and UtA-PI are not part of routine care and would be associated with an additional cost.

The objective of this study is to explore the possibility of carrying out first-stage screening in the whole population by maternal factors alone or a combination of maternal factors, MAP and UtA-PI or maternal factors, MAP and PlGF and proceeding to second-stage screening by a combination of maternal factors, MAP, UtA-PI and PlGF (triple test) only for a subgroup of the population selected on the basis of the risk derived from first-stage screening.

MATERIALS AND METHODS

Study population

The data for this study were derived from three previously reported prospective non-intervention screening studies at 11^{+0} - 13^{+6} weeks' gestation in a combined total of 61,174 singleton pregnancies, including 1,770 (2.9%) that developed PE. The first study involved 35,948 pregnancies in two maternity hospitals in England,[16] the second study, involved 8,775 pregnancies in 12 maternity hospitals in England, Spain, Belgium, Italy and Greece,[18] and the third study, involved 16,451 pregnancies in seven maternity hospitals in England.[7] Women with singleton pregnancies in the participating hospitals had a routine examination at 11^{+0} - 13^{+6} weeks' gestation. This visit included first, recording of maternal characteristics and medical history,[6] second, measurement of the left and right UtA-PI by transabdominal color Doppler ultrasound and calculation of the mean PI,[19] third, measurement of MAP by validated automated devices and standardized protocol,[20] and fourth, measurement of serum concentration of PlGF (DELFIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, USA or BRAHMS KRYPTOR analyzer, Thermo Fisher Scientific, Hennigsdorf, Germany). Gestational age was determined from the fetal crown-rump length.[21] The women gave written informed consent to participate in the studies, which were approved by the relevant research ethics committee in each participating country.

Patient characteristics including maternal age, racial origin (White, Black, South

Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs or *in vitro* fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus (SLE) or anti-phospholipid syndrome (APS), family history of PE in the mother of the patient and obstetric history including parity (parous or nulliparous if no previous pregnancies at or after 24 weeks), previous pregnancy with PE, gestational age at delivery and birth weight of the neonate in the last pregnancy and interval in years between birth of the last child and estimated date of conception of the current pregnancy. Maternal height and weight were measured. We have previously reported that increased risk for PE is provided by advancing maternal age, increasing weight, Black and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus and SLE or APS, conception by in vitro fertilization, family history of PE and personal history of PE; in the latter group the risk is inversely related to the gestational age at delivery of the previous pregnancy.[6] The risk for PE is decreased with increasing maternal height and in parous women with no previous PE; in the latter group, the maximum protective effect is when the interval between the current and previous pregnancy is 1-2 years, but the beneficial effect persists for more than 15 years.[6]

The inclusion criteria were singleton pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a morphologically normal live birth or stillbirth at $\geq$24 weeks' gestation. We excluded pregnancies

with aneuploidies and major fetal abnormalities and those ending in termination, miscarriage or fetal death at <24 weeks.

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy associated hypertension were examined to determine if the condition was PE, as defined by the International Society for the Study of Hypertension in Pregnancy.[22] The outcome measures for this study were early-PE and preterm-PE.

Statistical analysis

The competing risks approach is based on a survival-time model for the gestational age at delivery with PE.[6,16] In this approach it is assumed that if the pregnancy was to continue indefinitely all women would develop PE and whether they do so or not before a specified gestational age depends on competition between delivery before or after development of PE. The effects of variables from maternal factors and biomarkers is to modify the distribution of gestational age at delivery with PE so that in pregnancies at low risk for PE the gestational age distribution is shifted to the right with the implication that in most pregnancies delivery will actually occur before development of PE. In high-risk pregnancies the distribution is shifted to the left and the smaller the mean gestational age the higher is the risk for PE. Each woman has a personalized distribution of gestational age at delivery with PE and the risk of delivery with PE before a

specified gestational age, assuming no other cause delivery, is given by the area under the probability density curve. Bayes theorem is used to combine a *prior* distribution determined from maternal demographic and pregnancy characteristics with likelihoods from biomarkers to obtain the *posterior* distribution of time to delivery with PE.

The performance of screening for PE was assessed via a two-stage strategy (Figure 1). On the basis of the results of first-stage screening the population was divided into a low-risk, screen negative group and a higher-risk group in need of further testing. After such testing the patients were again classified as screen-negative and screen-positive. The performance of three first-stage strategies was examined: screening of the whole population by maternal factors alone, maternal factors, MAP and UtA-PI and maternal factors, MAP and PlGF. The second stage test was the triple test. The proportion of women continuing to the second-stage and the overall SPR and DR for preterm-PE and early-PE were defined by various stage 1 and stage 2 risk cut-offs.

The risk for development of PE is higher in women of Black or South Asian racial origin than in White women.[6] Consequently in screening in a population of mixed racial origins, for a given risk cut-off, the DR and SPR would be higher in Black and South Asian than White women and the overall performance would be dependent on the proportion of the various racial groups within that population. The majority of our patients were White (44,684 / 61,174) and therefore decided to

develop a stratification model based on our population of White women and then observe the performance of screening in different racial groups.

Predictive performance of two-stage risk stratification was assessed, and risk cut-offs were chosen, using previously published models and parameter estimates[6,16,17]. Empirical performance, for the sample of 61,174, using the same risk cut-off's was then compared with model predictions results. Model based predictions were obtained by simulation from the fitted model as follows. Maternal characteristics, medical history and outcomes from the 44,684 records on White women were sampled with replacement to generate a simulated population of 1,000,000 individuals. MoM values for MAP, UtA-PI and PlGF were then simulated from the fitted multivariate Gaussian distribution for log transformed MoM values for this population cohort.[16,17] Risks of PE with delivery <37 weeks were then calculated. This involved, for each individual, combining the maternal characteristic specific *prio*r distribution with the likelihood from the MoM values using Bayes theorem to obtain the *posterior* distribution of time to delivery with PE. Risks were obtained from this by computing the probability of PE with delivery <37 weeks. We chose to simulate a large population of 1,000,000 so that the imprecision in results induced by simulation was negligible. Risk cut-offs for the simulated data were selected so that the DR of preterm-PE was within 1% of that achieved by screening the whole population with the triple test.

Empirical performance was assessed by applying the risk calculations described

above to the sample of 61,174 using the original MoM values and applying the risk cut-offs obtained from the simulation. Performance was assessed using estimates and confidence intervals for the proportions continuing to the second stage, for the overall screen positive rate and detection rate.

The statistical software package R was used for data analyses.[23]

RESULTS

Characteristics of the study population

The characteristics of the study population are summarized in Table 1. The incidence of all PE, preterm-PE and early-PE were 2.9%, 0.8% and 0.2%, respectively. In the PE group, compared to the no PE group, there was a higher median BMI and interpregnancy interval and frequency of self-identified Black women, chronic hypertension, diabetes mellitus, family history of PE, artificial conception, nulliparity and previous pregnancy with PE; the incidence of smoking was lower.

Model-based performance of two-stage screening

The model-based DR of preterm-PE and early-PE in women of White racial origin, at SPR of 10%, 15% and 20% are shown in Tables 2-4, respectively. In screening

the whole population by the triple test, at SPR of 10%, the DR of preterm-PE was 67.0% and early-PE was 85.3%; the respective values at SPR of 15% were 75.6% and 90.1% and at SPR of 20% were 81.3% and 92.8%.

In two-stage screening with maternal factors as the method of screening in the first-stage and reserving measurements of MAP, UtA-PI and PlGF for the second-stage to only 70% of the population, a similar DR was achieved as in screening the whole population by the triple test, irrespective of whether the screen positive rate was 10%, 15% or 20% (Tables 2-4; Figure 2). In the case of first-stage screening by maternal factors, MAP and UtA-PI, a similar DR was achieved as in screening the whole population with the triple test, by reserving measurement of PlGF in the second-stage to only about 30% of the population for an overall SPR of 10% and 40% for SPR of 20%. In the case of first-stage screening by maternal factors, MAP and PlGF, a similar DR was achieved as in screening the whole population with the triple test, by reserving measurement of UtA-PI in the second-stage to only about 20% of the population for an overall SPR of 10% and 30% for SPR of 20%.

Empirical performance of two-stage screening

On the basis of the model-based results, we selected the following risk cut-offs for preterm-PE to assess the empirical performance of screening at SPR of 10%. For the first-stage the risk cut-offs for selecting the group in need for second stage

screening was 1 in 600 when screening was by maternal factors, 1 in 300 in screening by a combination of maternal factors, MAP and UtA-PI and 1 in 200 in screening or maternal factors, MAP and PlGF. The risk cut-off for selecting the screen positive group after second stage screening was 1 in 100.

Empirical performance of two-stage screening, at a fixed overall SPR of 10% for White women is shown in Table 5. At the selected risk cut-offs for first- and second-stage screening the proportion of the population requiring second-stage screening was about 70% when first-stage screening was by maternal factors, about 30% when first-stage screening was by a combination of maternal factors, MAP and UtA-PI and 20% for screening by maternal factors, MAP and PlGF. The observed DRs of preterm-PE were about 68% and for early-PE they were about 85% and these rates were consistent with the model-based rates.

At the same risk cut-offs for first- and second-stage screening as in White women, the overall SPR was about 35% for women of Black racial origin and about 16% for women of South Asian racial origin (Table 5). The proportion of Black and South Asian women requiring second-stage screening with each method of first-stage screening was considerably higher than in White women and the DR of preterm-PE was >90% and of early-PE it was >99%.

On the basis of the model-based results, we selected the following risk cut-offs for preterm-PE to assess the empirical performance of screening at SPR of 15%. For

the first-stage the risk cut-offs for selecting the group in need for second stage screening was 1 in 600 when screening was by maternal factors, 1 in 350 in screening by a combination of maternal factors, MAP and UtA-PI and 1 in 250 in screening or maternal factors, MAP and PlGF. The risk cut-off for selecting the screen positive group after second stage screening was 1 in 150. Empirical performance is shown in Table 6. In White women, the proportion of the population requiring second-stage screening was about 70% when first-stage screening was by maternal factors, about 40% when first-stage screening was by a combination of maternal factors, MAP and UtA-PI and about 25% for screening by maternal factors, MAP and PlGF. The observed DRs of preterm-PE and early-PE were about 80% and 90%, respectively.

On the basis of the model-based results, we selected the following risk cut-offs for preterm-PE to assess the empirical performance of screening at SPR of 20%. For the first-stage the risk cut-offs for selecting the group in need for second stage screening was 1 in 600 when screening was by maternal factors, 1 in 400 in screening by a combination of maternal factors, MAP and UtA-PI and 1 in 300 in screening or maternal factors, MAP and PlGF. The risk cut-off for selecting the screen positive group after second stage screening was 1 in 200. Empirical performance is shown in Table 7. In White women, the population requiring second-stage screening was about 70% when first-stage screening was by maternal factors, about 40% when first-stage screening was by a combination of maternal factors, MAP and UtA-PI and about 30% in screening by maternal

factors, MAP and PlGF. The observed DRs of preterm-PE and early-PE were about 80% and 90%, respectively.

COMMENT

Principal findings of this study

The findings of the study demonstrated that in screening a population of White women by the triple test at 11-13 weeks' gestation the DR of preterm-PE was 67% and that of early-PE was 85%, at SPR of 10%; the respective values at SPR of 20% were 81% and 93%. A similar performance can be achieved by a two-stage strategy whereby only some of the components of the triple test are used to screen the whole population and the other components are reserved for only a portion of the total population. If the method of first-stage screening is maternal factors, then measurements of MAP, UtA-PI and PlGF can be reserved for only 70% of the population. In the case of first-stage screening by maternal factors, MAP and UtA-PI, then measurement of PlGF can be reserved for only 30-40% of the population and if first-stage screening is by maternal factors, MAP and PlGF measurement of UtA-PI can be reserved for only 20-30% of the population.

In the application of Bayes theorem the maternal factor derived *prior* risk has a strong influence on the *posterior* risk and therefore the performance of screening. The risk of development of PE in women of Black or South Asian racial origin is higher than in White women [6] and therefore in screening for PE with the same risk cut-offs as in White women the SPR and DR in these racial groups are

considerably higher. Inevitably the overall performance of screening in a racially mixed population will depend on the proportion of the various racial groups. This is analogous to screening for Down syndrome where the maternal age derived *prior* risk is combined with the measurement of first- and or second-trimester biomarkers to derive the *posterior* risk; at a fixed risk cut-off, both the SPR and DR increase with maternal age and therefore the overall performance of screening depends of the maternal age distribution of a given study population.

Strengths and limitations

The strengths of this large screening study are first, recording of data on maternal characteristics and medical history to identify known risk factors associated with PE, second, use of a specific methodology and appropriately trained doctors to measure UtA-PI and MAP and automated machines to provide reproducible measurements of PlGF, third, expression of the values of the biomarkers as MoMs after adjustment for factors that affect the measurements, fourth, use of Bayes theorem to combine the *prior* distribution of gestational age at delivery with PE from maternal factors with biomarkers to estimate patient-specific risks and the performance of screening for PE delivering at different stages of pregnancy and fifth, comparison of model-based and empirical results on performance of screening.

The observed performance of two-stage screening apply to our study population and comparison between studies requires the appropriate adjustments for the

characteristics of the population under investigation. In the application of screening in different countries it is likely that adjustments would be necessary for the calculation of MoM values for the biomarkers and establishment of a system for quality assurance of the measurements.

Previous studies on two-stage screening

Previous studies have demonstrated that two-stage strategies provide a cost effective way of screening for Down syndrome; the performance of screening by a combination of first-trimester fetal nuchal translucency and first- and second-trimester serum biochemistry in all pregnancies, as in the integrated test, is similar to two-stage screening in which second-trimester testing is carried out in only about 25% of the population, identified by first-trimester screening as being at intermediate-risk.[24,25] Another screening study for Downs proposed that after first-trimester combined screening the population would be stratified into high-, intermediate- and low-risk groups; the high-risk group would have invasive testing and the intermediate-risk group would have second-stage screening with assessment of the fetal nasal bone and Doppler flow in the ductus venosus and across the tricuspid valve to identify another high-risk group in need of invasive testing.[26] More recently, a contingent strategy has been proposed for maternal blood cell-free DNA testing after the first trimester combined test.[27]

In relation to screening for PE, in a previous study we proposed a two-stage strategy in which first-stage screening in all pregnancies is based on maternal

factors and MAP at 11-13 weeks' gestation and on the basis of risks a group is selected for additional measurements of UtA-PI and PlGF.[28] The study reported that the model-based DR of preterm-PE achieved by screening the whole population with the triple test could also be achieved by reserving measurements of UtA-PI and PlGF to only 50% of the population.

Implications for clinical practice.

The need for effective first-trimester screening for preterm-PE has become apparent by recent evidence that in women identified by such screening as being at high-risk for PE administration of aspirin starting before 16 weeks' gestation reduces the rate of early-PE by about 90% and preterm-PE by 60%.[1,2] The prediction of PE provided by the traditional approach to screening, based on a series of maternal characteristics and medical history which are treated as independent risk factors, is poor. A prospective study comparing NICE guidelines with our competing risk model incorporating the triple test demonstrated that at the same SPR the DR of preterm-PE with our approach was twice as high.[7]

In screening by the triple test in a population of White women the DR of preterm-PE was 67%, at SPR of 10% and this increased to 76% at SPR of 15% and 81% at SPR of 20%. Randomized trials on the use of aspirin have reported that the drug is not associated with increased risk of adverse events and in the case of antepartum hemorrhage the risk may actually be reduced.[29] In this respect, it may be acceptable that in screening for PE the SPR could be 15% or even 20%

so as to maximize the DR. The inevitable consequence of fixing a risk cut-off aiming to achieve a given SPR in a White population is that the rate would be considerably higher for women of Black or South Asian racial origin. An alternative strategy in screening is to fix the SPR to be the same for all racial groups and using different risk cut-offs for each group; in a multiracial society such strategy would not be easy to implement and in any case, it would be wrong because it would merely mask the increased risk for PE in certain racial groups.

The findings of this study demonstrate that a similar SPR and DR can be achieved with a two-stage strategy of screening as with carrying out screening with all biomarkers in the whole population. Inevitably, biomarker screening for only part of the population will have financial benefits over conducting the test for the entire population. If the method of first-stage screening is maternal factors, then measurement of biomarkers can be reserved for only 70% of the population and if some of the biomarkers are included in first-stage screening then the need for the complete triple test can be reduced to 20-40% of the population.

REFERENCES

1. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017;377:613-22.

2. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol 2018;218:287-293.e1.

3. Wright D, Rolnik DL, Syngelaki A, et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol 2018;218:612.e1-612.e6.

4. National Collaborating Centre for Women's and Children's Health (UK). Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy. London: RCOG Press, 2010.

5. ACOG Committee Opinion No. 743 Summary: Low-Dose Aspirin Use During Pregnancy. Obstet Gynecol 2018;132:254-6.

6. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. Am J Obstet Gynecol 2015;213:62 e1-10.

7. Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. Ultrasound Obstet Gynecol 2018;51:743-50.

8. Gallo DM, Wright D, Casanova C, Campanero M, Nicolaides KH: Competing risks model in screening for preeclampsia by maternal factors and

biomarkers at 19-24 weeks' gestation. Am J Obstet Gynecol 2016;214:619.e1-619.e17.

9. Poon LC, Kametas NA, Chelemen T, Leal A, Nicolaides KH. Maternal risk factors for hypertensive disorders in pregnancy: a multivariate approach. J Hum Hypertens 2010;24:104-10.

10. Poon LC, Akolekar R, Lachmann R, Beta J, Nicolaides KH. Hypertensive disorders in pregnancy: screening by biophysical and biochemical markers at 11-13 weeks. Ultrasound Obstet Gynecol 2010;35:662-70.

11. Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. Prenat Diagn 2011;31:66-74.

12. Scazzocchio E, Figueras F, Crispi F, Meler E, Masoller N, Mula R, et al. Performance of a first-trimester screening of preeclampsia in a routine care low-risk setting. Am J Obstet Gynecol 2013;208:203.e1-.e10.

13. Baschat AA, Magder LS, Doyle LE, Atlas RO, Jenkins CB, Blitzer MG. Prediction of preeclampsia utilizing the first trimester screening examination. Am J Obstet Gynecol 2014;211:514.e1-7.

14. Wright D, Akolekar R, Syngelaki A, Poon L, Nicolaides KH. A competing risks model in early screening for preeclampsia. Fetal Diagn Ther 2012;32:171-8.

15. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. Fetal Diagn Ther 2013;33:8-15.

16. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Am J Obstet Gynecol 2016; 214:103.e1-103.e12.

17. Tan MY, Syngelaki A, Poon LC, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2018;52:186-95.

18. O'Gorman N, Wright D, Poon LC, et al. Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2017;49:751-5.

19. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11+0 to 13+6 weeks in the prediction of pre-eclampsia. Ultrasound Obstet Gynecol 2007;30:742-9.

20. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. Fetal Diagn Ther 2012;31:42-8.

21. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. Br J Obstet Gynaecol 1975;82:702-10.

22. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: Statement from the international society for the study of hypertension in pregnancy (ISSHP). Hypertens Pregnancy 2001;20:IX-XIV.

23. R Development Core Team. R. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2011;ISBN 3-900051-07-0, URL http://www.R-project.org/.

24. Wright D, Bradbury I, Benn P, Cuckle H, Ritchie K. Contingent screening for Down syndrome is an efficient alternative to non-disclosure sequential screening. Prenat Diag 2004;24:762-6.

25. Cuckle HS, Malone FD, Wright D, Porter TF, Nyberg DA, Comstock CH, Saade GR, Berkowitz RL, Ferreira JC, Dugoff L, Craigo SD, Timor IE, Carr SR, Wolfe HM, D'Alton ME. Contingent screening for Down syndrome--results from the FaSTER trial. Prenat Diag 2008;28:89-94.

26. Nicolaides KH, Spencer K, Avgidou K, Faiola S, Falcon O. Multicenter study of first-trimester screening for trisomy 21 in 75 821 pregnancies: results and estimation of the potential impact of individual risk-orientated two-stage first-trimester screening. Ultrasound Obstet Gynecol 2005;25:221-6.

27. Nicolaides KH, Wright D, Poon LC, Syngelaki A, Gil MM. First-trimester contingent screening for trisomy 21 by biomarkers and maternal blood cell-free DNA testing. Ultrasound Obstet Gynecol 2013;42:41-50.

28. Wright D, Gallo DM, Gil Pugliese S, Casanova C, Nicolaides KH. Contingent screening for preterm pre-eclampsia. Ultrasound Obstet Gynecol

2016;47:554-9.

29. Roberge S, Bujold E, Nicolaides KH. Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. Am J Obstet Gynecol 2018;218:483-9.

Table 1. Characteristics of the screening population.

Variable	No PE (n=59,404)	PE < 37 weeks (n=493)	PE < 32 weeks (n=116)	All PE (n=1,770)	p-value *
Maternal age in years, median (IQR	31.3 (27.1, 35.0)	32.1 (27.5, 36.0)	30.2 (25.9, 35.1)	31.45 (27.0, 35.3)	0.328
Maternal weight in kg, median (IQR)	66.6 (59.0, 77.0)	74.0 (63.4, 86.7)	74.8 (65.0, 89.6)	73.2 (63.1, 86.9)	<0.00001
Maternal height in cm, median (IQR)	165 (160, 169)	163 (158, 168)	163 (159, 167)	164 (159, 168)	<0.00001
Body mass index, median (IQR)	24.5 (21.9, 28.4)	27.5 (23.9, 32.9)	28.2 (24.1, 33.8)	27.4 (23.6, 32.4)	<0.00001
Gestational age in weeks, median (IQR)	12.7 (12.3, 13.1)	12.7 (12.3, 13.1)	12.6 (12.2, 13.1)	12.7 (12.3, 13.1)	0.137
Racial origin					<0.00001
White, n (%)	43,663 (73.5)	256 (51.9)	48 (41.4)	1,021 (57.7)	
Black, n (%)	9,539 (16.1)	183 (37.1)	56 (48.3)	569 (32.2)	
South Asian, n (%)	3,332 (5.6)	38 (7.7)	9 (7.8)	114 (6.4)	
East Asian, n (%)	1,383 (2.3)	4 (0.8)	0 (0.0)	24 (1.4)	
Mixed, n (%)	1,487 (2.5)	12 (2.4)	3 (2.6)	42 (2.4)	
Medical history					
Chronic hypertension	590 (1.0)	78 (15.8)	19 (16.4)	208 (11.8)	<0.00001
Diabetes mellitus, n (%)	470 (0.8)	17 (3.4)	4 (3.5)	30 (1.7)	<0.00001
SLE / APS, n (%)	104 (0.2)	5 (1.0)	0 (0.0)	7 (0.4)	0.062
Smoker, n (%)	5,000 (8.4)	30 (6.1)	6 (5.2)	100 (5.7)	0.00004
Family history of preeclampsia, n (%)	2,256 (3.8)	46 (9.3)	10 (8.6)	136 (7.7)	<0.00001
Method of conception					0.0015
Natural, n (%)	57,314 (96.5)	459 (93.1)	112 (96.6)	1,677 (94.7)	
In vitro fertilization, n (%)	1,572 (2.6)	23 (4.7)	2 (1.7)	72 (4.1)	
Ovulation drugs	517 (0.9)	11 (2.2)	2 (1.7)	21 (1.2)	
Parity					<0.00001
Nulliparous, n (%)	28,014 (47.2)	271 (55.0)	61 (52.6)	1,061 (59.9)	
Parous with no previous PE, n (%)	29,771 (50.1)	146 (29.6)	33 (28.4)	482 (27.2)	
Parous with previous PE, n (%)	1,619 (2.7)	76 (15.4)	22 (19.0)	227 (12.8)	
Pregnancy interval in years, median (IQR)	2.9 (1.8, 4.8)	4.6 (2.6, 7.6)	4.4 (2.3, 7.4)	4 (2.3, 6.8)	<0.00001

PE = preeclampsia; IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome. Please note that the all PE group includes all cases of PE <37 and PE <32 weeks and that the PE <37 weeks includes all cases of PE <32 weeks. *Comparisons between all PE and no PE groups were by chi-square or Fisher exact test for categorical variables and Mann Whitney-U test for continuous variables.

Table 2. Model-based performance of two-stage screening for preterm- and early-preeclampsia at overall screen positive rate of 10% in White women. First-stage screening is carried out in all pregnancies by maternal factors alone or a combination of maternal factors, MAP and UtA-PI or maternal factors, MAP and PlGF. Column 1 provides the proportion of the population proceeding to second stage screening which is carried out by the triple test. The grey boxes highlight the similarity in detection rate of preterm-preeclampsia between the triple test in all pregnancies and two-stage screening in which the triple test is reserved for only some women.

Proportion continuing to stage 2 (%)	First stage screening by history				First stage screening by history + MAP + UtA-PI				First stage screening by history + MAP + PlGF			
	Risk cut-offs		Detection rate of PE (%)		Risk cut-offs		Detection rate of PE (%)		Risk cut-offs		Detection rate of PE (%)	
	Stage 1	Stage 2	<37 w	<32 w	Stage 1	Stage 2	<37 w	<32 w	Stage 1	Stage 2	<37 w	<32 w
100	-	94	**67.0**	85.3	-	94	**67.0**	85.3	-	94	**67.0**	85.3
95	1876	94	67.0	85.3	6328	94	67.0	85.3	8477	94	67.0	85.3
90	1392	95	67.0	85.3	3731	94	67.0	85.3	4823	94	67.0	85.3
85	1089	95	67.0	85.3	2587	94	67.0	85.3	3285	94	67.0	85.3
80	884	95	67.0	85.3	1930	94	67.0	85.3	2408	94	67.0	85.3
75	703	96	66.7	84.4	1499	94	67.0	85.3	1846	94	67.0	85.3
70	560	96	**66.6**	84.6	1195	94	67.0	85.3	1456	94	67.0	85.3
65	437	98	66.1	83.0	969	94	67.0	85.3	1170	94	67.0	85.3
60	349	99	65.6	81.6	796	94	67.0	85.3	951	94	67.0	85.3
55	298	102	64.8	79.8	659	95	67.0	85.3	779	94	67.0	85.3
50	265	106	63.6	77.1	549	95	66.9	85.2	641	94	67.0	85.3
45	240	111	62.5	76.6	459	95	67.0	85.2	528	94	67.0	85.3
40	219	118	61.4	75	382	95	66.9	85.2	434	94	67.0	85.3
35	200	127	60.6	73.2	317	96	66.7	84.9	355	95	67.0	85.3
30	182	140	57.2	64.7	260	98	**66.7**	84.7	288	95	67.0	85.2
25	163	162	54.9	61.4	211	102	66.4	84.6	229	96	67.1	85.4
20	145	202	50.0	57.5	167	110	65.8	83.4	178	99	**67.0**	84.8
15	123	305	45.4	52	127	134	64.1	80.7	132	109	66.2	83.9

Table 3. Model-based performance of two-stage screening for preterm- and early-preeclampsia at overall screen positive rate of 15% in White women. First-stage screening is carried out in all pregnancies by maternal factors alone or a combination of maternal factors, MAP and UtA-PI or maternal factors, MAP and PlGF. Column 1 provides the proportion of the population proceeding to second stage screening which is carried out by the triple test. The grey boxes highlight the similarity in detection rate of preterm-preeclampsia between the triple test in all pregnancies and two-stage screening in which the triple test is reserved for only some women.

Proportion continuing to stage 2 (%)	First stage screening by history				First stage screening by history+MAP+UtPI				First stage screening by history+MAP+PlGF			
	Risk cut-offs		Detection rate		Risk cut-offs		Detection rate		Risk cut-offs		Detection rate	
	Stage 1	Stage 2	<37 w	<32 w	Stage 1	Stage 2	<37 w	<32 w	Stage 1	Stage 2	<37 w	<32 w
100	-	141	**75.6**	90.1	-	141	**75.6**	90.1	-	141	**75.6**	90.1
95	1876	141	75.5	90.1	6328	141	75.6	90.1	8477	141	75.6	90.1
90	1392	142	75.5	90.1	3731	141	75.6	90.1	4823	141	75.6	90.1
85	1089	142	75.4	90.0	2587	141	75.6	90.1	3285	141	75.6	90.1
80	884	143	75.4	90.1	1930	141	75.6	90.1	2408	141	75.6	90.1
75	703	144	74.9	88.8	1499	141	75.6	90.1	1846	141	75.6	90.1
70	560	146	**74.7**	88.8	1195	141	75.6	90.1	1456	141	75.6	90.1
65	437	149	74.3	87.2	969	141	75.6	90.1	1170	141	75.6	90.1
60	349	153	73.3	85.4	796	141	75.6	90.1	951	141	75.6	90.1
55	298	159	72.1	82.8	659	142	75.5	90.0	779	141	75.6	90.1
50	265	168	70.7	80.3	549	142	75.4	89.9	641	141	75.6	90.1
45	240	179	68.9	79.1	459	144	75.3	90.0	528	141	75.5	89.9
40	219	195	67.6	77.6	382	146	75.2	89.9	434	142	75.4	89.9
35	200	218	66.1	75.9	317	150	**75.0**	89.4	355	143	75.4	90.0
30	182	256	61.6	66.3	260	157	74.5	88.7	288	145	75.3	89.8
25	163	323	58.7	62.7	211	172	73.7	88.3	229	151	**75.3**	89.9
20	145	496	52.5	58.1	167	212	72.0	86.6	178	171	74.5	88.5

Table 4. Model-based performance of two-stage screening for preterm- and early-preeclampsia at overall screen positive rate of 20% in White women. First-stage screening is carried out in all pregnancies by maternal factors alone or a combination of maternal factors, MAP and UtA-PI or maternal factors, MAP and PlGF. Column 1 provides the proportion of the population proceeding to second stage screening which is carried out by the triple test. The grey boxes highlight the similarity in detection rate of preterm-preeclampsia between the triple test in all pregnancies and two-stage screening in which the triple test is reserved for only some women.

Proportion continuing to stage 2 (%)	First stage screening by history				First stage screening by history + MAP + UtA-PI				First stage screening by history + MAP + PlGF			
	Risk cut-offs		Detection rate of PE (%)		Risk cut-offs		Detection rate of PE (%)		Risk cut-offs		Detection rate of PE (%)	
	Stage 1	Stage 2	<37 w	<32 w	Stage 1	Stage 2	<37 w	<32 w	Stage 1	Stage 2	<37 w	<32 w
100	-	194	**81.3**	92.8	-	194	**81.3**	92.8	-	194	**81.3**	92.8
95	1876	194	81.3	92.9	6328	194	81.3	92.8	8477	194	81.3	92.8
90	1392	195	81.3	92.9	3731	194	81.3	92.8	4823	194	81.3	92.8
85	1089	196	81.2	92.8	2587	194	81.3	92.8	3285	194	81.3	92.8
80	884	197	81.2	92.9	1930	194	81.3	92.8	2408	194	81.3	92.8
75	703	200	80.6	91.4	1499	194	81.3	92.8	1846	194	81.3	92.8
70	560	203	**80.3**	91.4	1195	194	81.3	92.9	1456	194	81.3	92.8
65	437	209	79.5	89.5	969	194	81.3	92.9	1170	194	81.3	92.8
60	349	217	78.3	87.7	796	195	81.4	92.9	951	194	81.3	92.8
55	298	229	76.9	85.0	659	196	81.4	92.8	779	194	81.3	92.8
50	265	246	75.2	82.1	549	198	81.2	92.7	641	194	81.3	92.9
45	240	269	72.8	80.8	459	201	81	92.6	528	195	81.3	92.8
40	219	303	71.1	78.5	382	208	**80.7**	92.6	434	197	81.3	92.8
35	200	356	69.1	76.5	317	220	79.9	91.7	355	201	81.1	92.6
30	182	454	64.4	66.9	260	243	79.0	90.7	288	211	**80.9**	92.4
25	163	700	60.6	63.0	211	302	77.7	89.8	229	241	80.4	91.7

Table 5. Empirical and model-based performance of two-stage screening at 11-13 weeks' gestation for preeclampsia (PE) with delivery at <37 and <32 weeks' gestation, at a fixed overall screen positive rate of 10% for White women, in the population subdivided according to racial origin. Second-stage screening is by a combination of maternal factors, MAP, UtA-PI and PlGF. The risk cut-off for preterm PE for selecting the group in need for second-stage screening is 1 in 600 when first-stage screening is by maternal factors and 1 in 300 when screening is by a combination of maternal factors, MAP and UtA-PI and 1 in 200 in screening by maternal factors, MAP and PlGF. The risk cut-off for selecting the screen positive group after second-stage screening is 1 in 100. The numbers in bold are the model-based values for White women.

Method of 1st stage screening	**Racial group**	**Need for 2nd stage screening (%)**	**Screen positive rate, % (95% CI)**	**Detection rate of preeclampsia, % (95% CI)**	
				<37 weeks	**<32 weeks**
Maternal factors	White	**71.4**	**10.4**	**67.6**	**85.0**
		71.4	10.2 (9.9, 10.5)	67.6 (61.5, 73.3)	83.3 (69.8, 92.5)
	Black	98.8	34.0 (33.0, 34.9)	92.3 (87.5, 95.8)	100 (93.6, 100)
	South Asian	88	16.5 (15.3, 17.8)	97.4 (86.2, 99.9)	100 (66.4, 100)
Maternal factors + MAP + UtA-PI	White	**33.6**	**10.3**	**67.4**	**85.2**
		34.7	10.1 (9.8, 10.4)	68.8 (62.7, 74.4)	85.4 (72.2, 93.9)
	Black	68.8	33.5 (32.6, 34.5)	92.3 (87.5, 95.8)	100 (93.6, 100)
	South Asian	47.6	16.2 (15.0, 17.5)	97.4 (86.2, 99.9)	100 (66.4, 100)
Maternal factors + MAP + PlGF	White	**22.2**	**10.3**	**67.5**	**85.5**
		21.6	10.1 (9.8, 10.4)	67.2 (61.1, 72.9)	85.4 (72.2, 93.9)
	Black	54.4	33.7 (32.8, 34.7)	91.8 (86.8, 95.3)	100 (93.6, 100)
	South Asian	30.3	16.3 (15.1, 17.6)	97.4 (86.2, 99.9)	100 (66.4, 100)

Table 6. Empirical and model-based performance of two-stage screening at 11-13 weeks' gestation for preeclampsia (PE) with delivery at <37 and <32 weeks' gestation, at a fixed overall screen positive rate of 15% for White women, in the population subdivided according to racial origin. Second-stage screening is by a combination of maternal factors, MAP, UtA-PI and PlGF. The risk cut-off for preterm PE for selecting the group in need for second-stage screening is 1 in 600 when first-stage screening is by maternal factors and 1 in 350 when screening is by a combination of maternal factors, MAP and UtA-PI and 1 in 250 in screening by maternal factors, MAP and PlGF. The risk cut-off for selecting the screen positive group after second-stage screening is 1 in 150. The numbers in bold are the model-based values for White women.

Method of 1st stage screening	**Racial group**	**Need for 2nd stage screening (%)**	**Screen positive rate, % (95% CI)**	**Detection rate of preeclampsia, % (95% CI)**	
				<37 weeks	**<32 weeks**
Maternal factors	White	**71.4**	**15.5**	**75.5**	**89.3**
		71.4	15.2 (14.8, 15.5)	78.1 (72.6, 83)	89.6 (77.3, 96.5)
	Black	98.8	43.3 (42.3, 44.3)	95.6 (91.6, 98.1)	100 (93.6, 100)
	South Asian	88.0	22.6 (21.2, 24.1)	97.4 (86.2, 99.9)	100 (66.4, 100)
Maternal factors + MAP + UtA-PI	White	**37.7**	**15.2**	**75.5**	**89.9**
		39.0	15.0 (14.7, 15.4)	80.1 (74.7, 84.8)	93.8 (82.8, 98.7)
	Black	72.6	42.7 (41.7, 43.7)	95.6 (91.6, 98.1)	100 (93.6, 100)
	South Asian	52.5	22.3 (20.9, 23.7)	97.4 (86.2, 99.9)	100 (66.4, 100)
Maternal factors + MAP + PlGF	White	**26.9**	**15.1**	**75.6**	**90.1**
		26.2	14.9 (14.6, 15.2)	78.1 (72.6, 83.0)	87.5 (74.8, 95.3)
	Black	59.9	42.8 (41.8, 43.7)	94.5 (90.2, 97.3)	100 (93.6, 100)
	South Asian	35.9	22.4 (21.0, 23.8)	97.4 (86.2, 99.9)	100 (66.4, 100)

Table 7. Empirical and model-based performance of two-stage screening at 11-13 weeks' gestation for preeclampsia (PE) with delivery at <37 and <32 weeks' gestation, at a fixed overall screen positive rate of 20% for White women, in the population subdivided according to racial origin. Second-stage screening is by a combination of maternal factors, MAP, UtA-PI and PlGF. The risk cut-off for preterm PE for selecting the group in need for second-stage screening is 1 in 600 when first-stage screening is by maternal factors, 1 in 400 when screening is by a combination of maternal factors, MAP and UtA-PI and 1 in 300 in screening by maternal factors, MAP and PlGF. The risk cut-off for selecting the screen positive group after second-stage screening is 1 in 200. The numbers in bold are the model-based values for White women.

Method of 1st stage screening	**Racial group**	**Need for 2nd stage screening (%)**	**Screen positive rate, % (95% CI)**	**Detection rate of preeclampsia, % (95% CI)**	
				<37 weeks	**<32 weeks**
Maternal factors	White	**71.4**	**19.8**	**80.3**	**91.3**
		71.4	19.5 (19.2, 19.9)	80.5 (75.1, 85.1)	89.6 (77.3, 96.5)
	Black	98.8	50.3 (49.4, 51.3)	98.3 (95.3, 99.7)	100 (93.6, 100)
	South Asian	88.0	28.6 (27.1, 30.2)	97.4 (86.2, 99.9)	100 (66.4, 100)
Maternal factors + MAP + UtA-PI	White	**41.3**	**19.6**	**80.5**	**92.2**
		42.4	19.4 (19.0, 19.8)	82.8 (77.6, 87.2)	93.8 (82.8, 98.7)
	Black	75.8	49.5 (48.5, 50.5)	97.8 (94.5, 99.4)	100 (93.6, 100)
	South Asian	56.3	28.3 (26.8, 29.8)	97.4 (86.2, 99.9)	100 (66.4, 100)
Maternal factors + MAP + PlGF	White	**31.0**	**19.4**	**80.5**	**92.1**
		30.3	19.2 (18.8, 19.5)	81.2 (75.9, 85.8)	89.6 (77.3, 96.5)
	Black	64.4	49.5 (48.6, 50.5)	97.3 (93.7, 99.1)	100 (93.6, 100)
	South Asian	40.4	27.8 (26.3, 29.3)	97.4 (86.2, 99.9)	100 (66.4, 100)

FIGURE LEGENDS

Figure 1. Two stage screening for preterm preeclampsia.

Figure 2. Relationship between model-based detection rate of preeclampsia with delivery at <37 weeks' gestation (black curve), <34 weeks (blue curve) and <32 weeks (red curve) and percentage of the population requiring second-stage screening at a fixed overall screen positive rate of 20% in women of White racial origin.

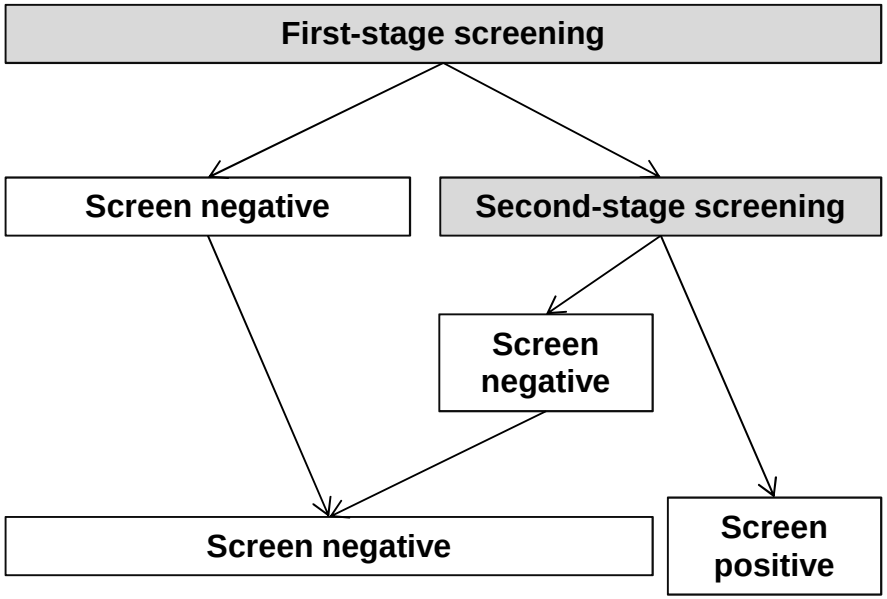

Figure 1

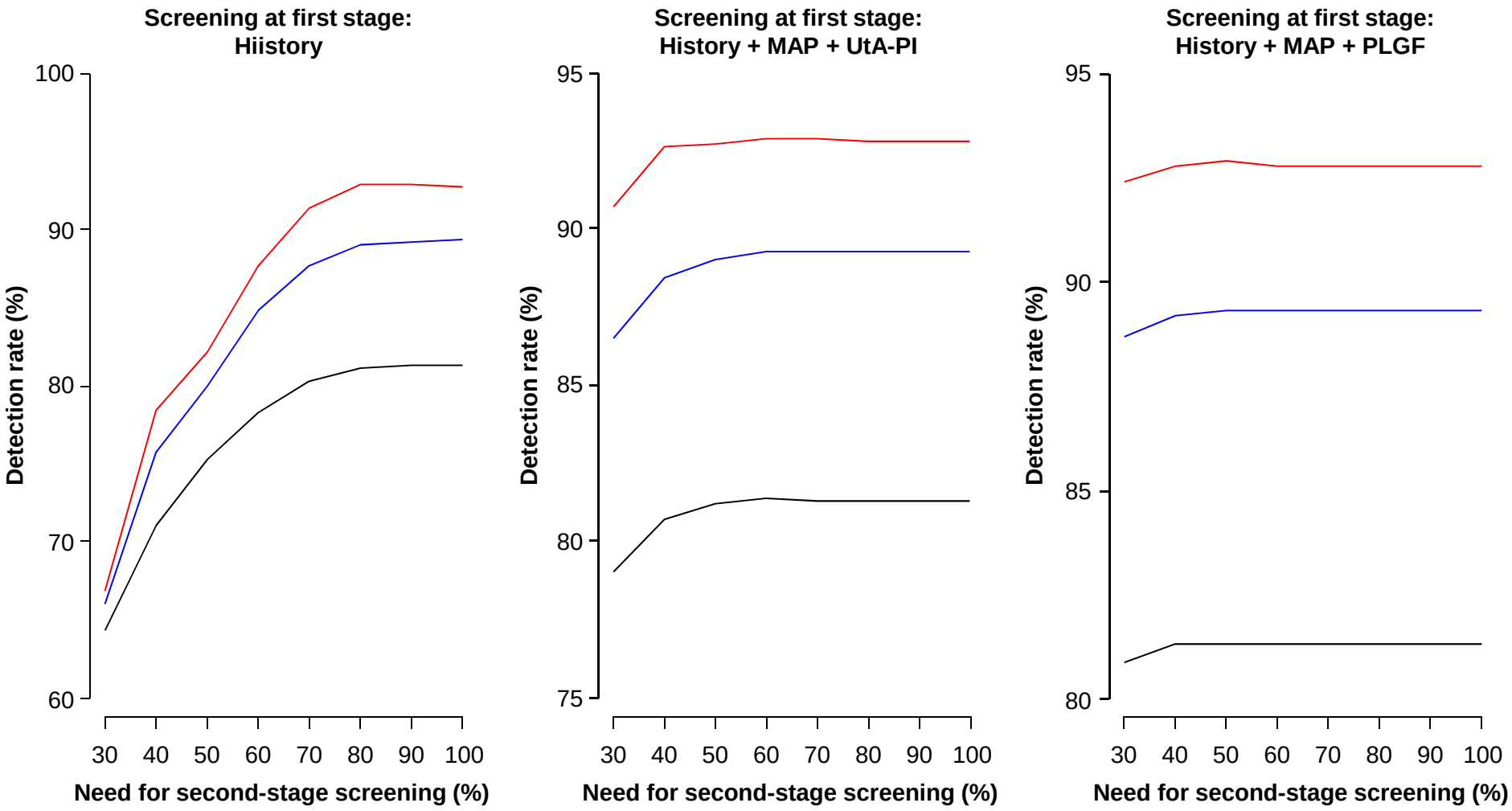

Figure 2